

**In the Specification:**

Please amend the specification as shown:

Please delete the paragraph on page 6, lines 9-12, and replace it with the following paragraph:

**Fig. 6:** is a list of oligonucleotide mismatch primers (SEQ ID NOS 11-13, respectively in order of appearance) used in accordance with the invention, where the underlined nucleotide indicates the sequence mismatch.

Please delete the paragraph on page 6, lines 14-16, and replace it with the following paragraph:

**Fig. 7:** is an illustration of the nucleotide sequence (SEQ ID NO: 19) of the 5' flanking region relative to the DNA sequence encoding CYP3A5.

Please delete the paragraph on page 6, lines 33-35, to page and replace it with the following paragraph:

**Fig. 9-9d:** are illustrations of the results obtained from the >find patterns= program of the GCG sequence analysis package (SEQ ID NOS 20-24, respectively in order of appearance in Figure 9, SEQ ID NO: 25 in Fig. 9(a), SEQ ID NO: 26 in Fig. 9(b), SEQ ID NO: 27 in Fig. 9(c), and SEQ ID NO: 28 in Fig 9(d)).

Please delete the paragraph on page 9, lines 7-10, and replace it with the following paragraph:

In this embodiment an example of suitable primers is any of 3A5F1 GGGTCTGTCTGGCTGCGC (SEQ ID NO: 11) and 3A5F2 (GGGGTCTGTCTGGCTGAGC) (SEQ ID NO: 12) and 3A5R1 (TTTATGTGCTGGAGAAGGACG) (SEQ ID NO: 13).

Please delete the paragraph on page 18, line 20, to page 19, line 4, and replace it with the following paragraph:

***Sequencing of the CYP3A5 5' flanking region***

A 1343 bp 5' flanking region of CYP3A5 was PCR amplified from genomic DNA isolated from liver samples, using primers 3A51 (5'-GGAAGCAACCTACATGTCCATC) (SEQ ID NO: 1) and 3A52 (5'-ATCGCCACTTGCCTTCTTC) (SEQ ID NO: 10) based on the published sequence of Jounaidi et al. (11). PCR conditions were 1 cycle of 95EC for 1 min, 30 cycles of 95EC for 1 min, 57EC for 30 sec, 72EC for 2.5 min, and 1 cycle of 72EC for 10 min. PCR products were purified using a QIAquick PCR Purification Kit (QIAGEN), sequencing primers were designed (Table 1), and used to directly sequence the PCR product on both sense and antisense strands by cycle sequencing using the ABI BigDye Terminator cycle sequencing kit (Perkin Elmer). Sequencing reactions were analysed on an ABI 377 automated sequencer. Contig sequences were aligned and compared using the Sequence Editor version 1.0.3 software packages (Perkin Elmer) and manually edited for identification of heterozygote positions.

Please delete the paragraph on page 19, lines 6-18, and replace it with the following paragraph:

***PCR detection assays for the A<sub>147</sub>G and T<sub>475</sub>G mutations***

All PCR assays were performed utilising a 1 in 100 dilution of the original 3A51/3A52 PCR product as template, under the following conditions: 1 cycle of 95EC for 1 min, 30 cycles of 95EC for 1 min, 55EC for 30 sec, 72EC for 1 min, and 1 final cycle of 72EC for 10 min. All products were sequenced to confirm the identity of the product as CYP3A5. Oligonucleotide mismatched primers utilised in the assays were: 3A5F1 (5'-GGGTCTGTCTGGCTGCGC) (SEQ ID NO: 11), 3A5F2 (5'-GGGGTCTGTCTGGCTGAGC) (SEQ ID NO: 12), and 3A5R1 (5'-TTTATGTGCTGGAGAAGGACG) (SEQ ID NO: 13), where positions of mismatches are underlined.

Please delete the paragraph on page 20, line 9, to page 21, line 4, and replace it with the following paragraph:

***Relative quantification and comparison of CYP3A5 RNA***

Relative levels of CYP3A5 mRNA were determined by real time PCR using the ABI 7700 SDS (Perkin Elmer). Optimal primers and probes for the detection of CYP3A5 were designed using the PrimerExpress program, and subsequently checked to ensure specificity for CYP3A5. Primers utilised for the quantification PCR were: forward - 5'-AAGTGGCGATGGACCTCATC-3' (SEQ ID NO: 14); reverse - 5'-GAGGAGCACCAGGCTGACA-3' (SEQ ID NO: 15). The TaqMan probe was labelled with the 5' reporter dye 6-carboxy-flouresine (FAM), and had the sequence 5'-CAAATTTGGCGGTGGAACCTGGC-3' (SEQ ID NO: 16). Optimal primer/probe ratios and concentrations were determined and the experiments run according to standard protocols for the ABI 7700 Standard Detection System. CYP3A5 mRNA expression for all samples was normalised against the expression of  $\beta$ -actin mRNA. The threshold cycle (Ct) is the PCR cycle number where the ABI 7700 begins to detect an increase in fluorescent signal associated with the linear amplification of PCR product. The Ct value is dependent on the initial amount of template copy. Quantities of CYP3A5 in each sample were determined by averaging the Ct from 3 separate PCR

reactions of each sample. Relative differences in Ct between samples were calculated by subtracting the Ct of each sample from the highest Ct within the samples (lowest expression). Since the amount of PCR product doubles with every cycle in the linear range of a PCR the differences in Ct were converted into estimated differences of mRNA quantity between the samples by calculating  $2^{\delta Ct}$ , where  $\delta Ct$  is the difference in cycle threshold between two samples.

Please delete the paragraph on page 30, lines 11-31, and replace it with the following paragraph:

**Electrophoretic mobility shift assay (EMSA)**

An EMSA was carried out using the Sp1 NUSHIFT Kit from Geneka Biotechnology Inc. (Montreal, Canada) according to the manufactures instructions. Briefly, a 31-mer double-stranded oligonucleotide corresponding to the CYP3A5 5'-untranslated region containing the A<sub>147</sub>G polymorphism (5'-GGC AGC TGC AGC CCC GCC TCC TTC TCC AGC A-3') (SEQ ID NO: 17) was end-labeled with <sup>32</sup>-P using T4 polynucleotide kinase. 50,000 cpm (0.5 ng) oligonucleotide was incubated with 2 µg HeLa nuclear extract for 30 min at 16°C. Unlabeled mutant or wildtype (5'-GGC AGC TGC AGC CCC ACC TCC TTC TCC AGC A-3') (SEQ ID NO: 18) oligo nucleotide was added in 50-fold or 100-fold excess as indicated. 1 or 2 µl anti-Sp1 rabbit polyclonal antibody was pre-incubated with the nuclear extract at 4°C for 30 min as indicated. Nuclear extract, anti-Sp1 antibody and binding buffers were from Geneka Biotechnology Inc. Samples were separated on a 5% polyacrylamide (39:1) gel, in TGE buffer (25 mM Tris, 190 mM glycine, 1 mM EDTA, pH 8.3). The dried gel was exposed to X-ray film.

Please delete Table 1 on page 38, and replace it with the following Table:

**Table 1.** Primers used for sequencing 5' flanking region of CYP3A5 from PCR product 3A51/3A52 (see text).

Primer	Orientation #	Position*	Sequence (5'-3')
3A51	F	-1237 <sub>6</sub> -1217	GGAAGCAACCTACATGTCCATC (SEQ ID NO: 1)
3A5p01	F	-978 <sub>6</sub> -963	AGTACAGGGAGCACAG (SEQ ID NO: 2)
3A5p08	R	-917 <sub>6</sub> -932	CACCTATTCATTCCTG (SEQ ID NO: 3)
3A5p02	F	-698 <sub>6</sub> -684	TGCTATCACCACAGAC (SEQ ID NO: 4)
3A5p07	R	-689 <sub>6</sub> 704	GGTGATAGCAATAGAC (SEQ ID NO: 5)
3A5p03	F	-364 <sub>6</sub> -349	AGGATGTGTAGGAGTC (SEQ ID NO: 6)
3A5p06	R	-417 <sub>6</sub> -434	CCTCACACAGATGTAACC (SEQ ID NO: 7)
3A5p04	F	-176 <sub>6</sub> -161	TAAGAACTCAGGTTCC (SEQ ID NO: 8)
3A5p05	R	-178 <sub>6</sub> -194	CAGAAACTGAAGTGGAG (SEQ ID NO: 9)
3A52	R	+105 <sub>6</sub> +87	ATCGCCACTTGCCTTCTTC (SEQ ID NO: 10)

# F = 5' to 3', R = 3' to 5'

\* Primer locations are based on CYP3A5 sequence data of Jounaidi et al (11)